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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	09/633,145
Filing Date	August 4, 2000
First Named Inventor	Chinnappa Kodira
Art Unit	1647
Examiner Name	WEGERT, Sandra L.
Attorney Docket Number	CL000747

Total Number of Pages in This Submission

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Technology Center (TC)
- [x] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Lin Sun-Hoffman, Ph.D., Reg. No.: 47,983
Signature	
Date	March 26, 2004

CERTIFICATE OF TRANSMISSION/MAILING

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PTO/SB/17 (10-03)
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FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 330

Complet if Kn wn	
Application Number	09/633,145
Filing Date	August 4, 2000
First Named Inventor	Chinnappa KODIRA et al.
Examiner Name	WEGERT, S.L.
Art Unit	1647
Attorney Docket No.	CL000747

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 50-0970

Deposit Account Name: CELERA GENOMICS

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, **except for the filing fee** to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($)

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below	Fee Paid
Total Claims		-20** =		X =
Independent Claims		- 3** =		X =
Multiple Dependent				=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	330
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 330

SUBMITTED BY				(Complete *(if applicable)*)	
Name (Print/Type)	Lin Sun-Hoffman, Ph.D.	*Registration No. (Attorney/Agent)*	47,983	*Telephone*	240-453-3628
Signature				*Date*	March 26, 2004

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This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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BEFORE THE BOARD OF PATENT APPEALS & INTERFERENCES
IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of:	
Chinnappa Kodira	Art Unit: 1647
Application No. 09/633,145	Examiner: Sandra Wegert
Filed: August 4, 2000	
For: ISOLATED HUMAN G-PROTEIN COUPLED RECEPTORS THAT ARE MEMBERS OF THE AMINERGIC SUBFAMILY, NUCLEIC ACID MOLECULES ENCODING HUMAN GPCR PROTEINS, AND USES THEREOF	Atty. Docket No. CL000747

BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTENTION: MAIL STOP APPEAL BRIEF - PATENTS

Sir:

This BRIEF ON APPEAL is filed, in triplicate, pursuant to a timely Notice of Appeal, filed February 5, 2004.

Real Party in Interest

The application is assigned to APPLERA CORPORATION.

Related Appeals and Interferences

There are no related appeals or interferences pending and applicants are not aware of any

previous appeals or interferences related to the present application or subject matter therein.

Status of the Claims

The application was originally filed with claims 1 - 23. The claims were subject to a restriction in Paper No. 8 (10/30/01). Applicants elected the invention of claims 4, 8, 9, 22 and 23 directed to the nucleic acid molecules, vectors, host cells, etc. in a response filed November 20, 2001. In that response applicants canceled claims 1-3, 5-7, 10-12 and 14-23 which had been determined to be directed to the non-elected invention and additionally added new claims 24-29. In the Office action of December 19, 2001 (Paper No. 11), the examiner acknowledged entry of that amendment and acknowledged that newly presented claims 24-29 were also drawn to the elected invention. However, the examiner did withdraw claim 13 as being directed to the non-elected invention. Claim 30 was added by amendment in the response filed October 9, 2002.

Thus, claims 4, 8, 9, 13, and 24-30 are pending in the application. Claim 13 stands withdrawn from consideration by the examiner and claims 4, 8, 9, and 24-30 stand rejected under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph.

Status of Amendments

No amendment after final was filed. All amendments filed prior to the final rejection has been entered.

Summary of the invention:

The invention disclosed and described in this application relates to an isolated nucleic acid molecule having the nucleic acid sequences that encode the amino acid sequences of human G-Protein coupled receptors (GPCR), allelic variants thereof and other mammalian orthologs thereof. These peptides and nucleic acid sequences have many application as described in the

present Specification. Both the isolated nucleic acid molecule and the proteins which they encode play a material and significant role in the mammalian physiology as described in the Specification.

Issues

Claims 4, 8, 9, and 24-30 stand finally rejected under 35 U.S.C. § 101 as lacking a substantial or specific utility and under 35 U.S.C. § 112, first paragraph as failing to provide an enabling disclosure.

The issue presented for this appeal is whether the examiner has improperly rejected the pending claims given the disclosure provided by the Specification relating to the claimed invention and the specific facts in this application.

Grouping of claims

All claims are subject to both rejections of record. Applicants have not separately addressed the patentability or the application of these two rejections to individual claims. Therefore, for purposes of this appeal, applicants would agree, that as to each rejection, the claims stand or fall together.

Arguments

In responding to the rejection of the pending claims under both 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, applicants would urge that the first step is to determine exactly what is being claimed. Claim 4, is an independent claim, directed to an isolated nucleic acid molecule consisting of a sequence which is to be selected from the three possible sequences defined by a nucleotide sequence that encodes a protein comprising the amino acid sequence of SEQ ID NO: 2; a nucleotide sequence consisting of the nucleic acid sequence of SEQ ID NO:1; and a nucleotide sequence consisting of the nucleic acid sequence of SEQ ID NO:3. Claim 8 is directed to a vector

comprising a nucleic acid as claimed in claim 4. Claim 9 is directed to a host cell containing the vector of claim 8. Claim 24 is directed to a process for producing a polypeptide comprising culturing the host cell of claim 9 under conditions sufficient for the production of said polypeptide from a nucleic acid molecule that encodes said polypeptide, and recovering said polypeptide from the host cell culture. Claim 25 is directed to an isolated polynucleotide consisting of a nucleotide sequence set forth in SEQ ID NO:1. Claim 26 is directed to an isolated polynucleotide consisting of a nucleotide sequence set forth in SEQ ID NO:3. Claim 27 is directed to a vector according to claim 8, wherein said vector is selected from the group consisting of a plasmid, virus, and bacteriophage. Claim 28 is directed to a vector according to claim 8, wherein said isolated nucleic acid molecule is inserted into said vector in proper orientation and correct reading frame such that the protein of SEQ ID NO:2 which may be expressed by a cell transformed with said vector. Claim 29 is directed to a vector according to claim 28, wherein said isolated nucleic acid molecule is operatively linked to a promoter sequence. Claim 30 is directed to an isolated nucleic acid molecule consisting of a nucleotide sequence that is completely complementary to a nucleotide sequence of claim 4.

Thus, all of the claims are directed either to a specific molecule having a defined nucleotide sequence or to a vector comprising the nucleotide molecule, a host cell which includes the nucleotide molecule, a process for producing a polypeptide using the nucleotide molecule or to a nucleotide molecule which is complementary to that nucleotide molecule claimed in independent claim 4.

The Rejection under 35 U.S.C. § 101:

The Examiner has finally rejected claims 4, 8, 9, and 24-30 under 35 U.S.C. § 101 as

lacking utility.

In the Final rejection the Examiner references the reasoning set forth at pages 2-9 in the Office action (OA) of December 16, 2002, Paper No. 20. Starting at page 3 of Paper No. 20 the Examiner states:

The claims are directed to recombinant expression of the peptide encoded by SEQ ID NO: 2, the nucleic acids encoding SEQ ID NO: 2 and complementary nucleic acids.

The Examiner concludes that:

No well established utility exists for newly-isolated complex biological molecules. However, the specification asserts the following as credible, specific and substantial patentable utilities for the claimed polypeptide and the polynucleotides and recombinant methods used to express it.

The Examiner then lists a series of utilities, acknowledged to be present in the Specification and addresses each in turn. (OA, pages 3-5).

As to the utility relating to the production of antibodies, the examiner acknowledges that the utility is credible and substantial, but urges that it is not specific. The Examiner acknowledges that antibodies can be made to any polypeptide, but urges that is the specification discloses nothing specific and substantial about the polypeptide, both the polypeptide and its antibodies have no patentable utility.

As to making of hybridization probes and primers to detect nucleic acid molecules that encode the polypeptide of SEQ ID NO: 2 and to localize receptor expression in tissue samples, the Examiner acknowledges that this utility is credible, but urges that it is not substantial or specific since the specification does not disclose specific cDNA, DNA or RNA targets and since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, and therefore is not substantial. (OA, page 4).

As to the search for drugs as ligands or antagonists of the polypeptide encoded by the

claimed polynucleotide, the Examiner acknowledges that this utility if credible and specific, but urges that it is not substantial since the specification does not characterize the polypeptide encoded by the polynucleotide of the claimed invention. Therefore the Examiner urges that binding sites, etc. are not identified and therefore further experimentation would be required of the skilled artisan to characterize the protein and search for the ligands. The Examiner notes that "[t]here is no disclosure for example, of how to assay for ligand binding and possible transduction mechanisms. It is not known the class of drugs to use or what measurements to perform. Since this asserted utility is not present in mature form so it could be readily used in the real world sense, the asserted utility is not substantial." (OA, page 4).

As to the production of variant or chimeric nucleotide or polypeptides, the Examiner acknowledges that this is a credible utility but urges that it is not substantial or specific since such assays can be performed with any polynucleotide and the specification discloses nothing specific or substantial for the variant nucleotide and polypeptide that is produced by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

As to the creation of transgenic animals, the Examiner acknowledges that the utility is credible, but urges that it is not specific or substantial since the specification does not disclose diseases associated with a mutated, deleted, or translocated gene of the present invention. The Examiner urges that "[s]ignificant further experimentation would be required of the skilled artisan to identify such a disease. The specification discloses nothing about whether the claimed gene will be "knocked in" or knocked out" or what specific tissues and cells are being targeted." The Examiner, again, concludes that since the asserted utility is also not present in mature form, so that

it could be readily used in the real world, the asserted utility is not substantial. (OA, page 5).

As to the detection of polymorphisms in individuals, the Examiner acknowledges that the utility is credible, however urges that it is neither specific nor substantial since the applicants have not demonstrated the function of the polypeptide encoded by the claimed polynucleotide, much less relevant polymorphisms. The Examiner also points out that there are many unrelated sequences which can be polymorhphic generally and therefore the utility is not specific. (OA, page 5).

As to the use of the claimed invention for clinical therapy using the polypeptide or ligand, the Examiner acknowledges that the utility is credible, but urges that it is not specific or substantial since it could be performed with any polypeptide and the specification does not disclose diseases associated with the gene of the claimed invention or with the polypeptide encoded by the gene. The Examiner notes that:

"[s]ignificant further experimentation would be required of the skilled artisan to identify individuals with such a disease and to determine the route of administration of the polypeptide or ligand, as well as quantity and duration of treatment." The Examiner concludes that since the asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

In the Final rejection of August 5, 2003 (Paper No. 23), the Examiner expands on this reasoning and explanation.

In the paragraph bridging pages 2-3 of the Final rejection, the Examiner acknowledges that:

[t]he claims are directed to a nucleotide that encodes a protein that possess approximately 100% homology to a known and well-characterized tyramine receptor, *Tar 1* (Bunzow, et al. 2001, Mol. Pharmacol., 60:1181-1188; Bunzow et al., 2003, et al., 2003, Accession No. NM_138327). The *Tar1* receptor has been studied extensively, and has a unique and specific pharmacological and physiological profile establishing it among the "trace-amine" receptors that respond to tyramine or phenethylamine (Bunzow, et al, 2001, see Figure 2A). As suggested by Bunzow, et al, such receptors are partly responsible for the severe parasnympathetic stimulation seen after ergot poisoning.

Following this acknowledgement that the protein encoded by the claimed nucleic acid has approximately 100% homology with a known and well characterized protein which is a tyramine receptor, the Examiner states that "no well-established utility exists for newly isolated complex biological molecules."

The Examiner notes that (OA, page 3):

[t]he specification does not discuss evidence nor disclose experiments that impart *any* function for the polypeptide encoded by the claimed nucleotides in the context of the cell or organism. The examiner notes the discussion, present in the Specification at page 2, first paragraph and page 4, first paragraph, which described applicants' understanding of the nature of the encoded protein and its activity as a member of the G-protein-coupled receptor family.[1]

The Examiner notes that (Final Rejection, paragraph bridging pages 3-4):

[t]he specification does not teach the skilled artisan how to use the receptor encoded by the claimed polynucleotide for any unique or specific purpose. Furthermore, the Specification, *as originally filed*, does not anticipate or even suggest that the disclosed receptor functions as a tyramine receptor like that disclosed and studied by Bunzow, et al. (2001, Mol. Pharmacol., 60: 1181-1188). For example there is no disclosure of specific ligands for the receptor, or of the anticipated changes in receptor-mediated processes in transfected cells, or the probable phenotypes of "knock-in" or "knock-out" organisms or of a specific caused by an overactivity or underactivity of the receptor.

Applicants' Response:

In rejecting claims 4, 8, 9, and 24-30 under 35 U.S.C. § 101, the examiner has attempted to address the extensive list of uses which the specification provides for both the claimed nucleotide molecule of defined sequence which is claimed as well as the protein which this nucletotide sequence encodes. However, in doing so, applicants would urge that the Examiner has

[1]Applicants would note that there is extensive discussion about the relationship of the protein which is encoded by the nucleic acid molecules of the present invention through out the specification and the two portions noted by the examiner are merely representative of the full disclosure.

misinterpreted both the law governing the utility requirement 35 U.S.C. § 101 as well as the facts in this particular application.

Applicants recognize that 35 U.S.C. § 101 requires that an invention must be both new and useful. The subject of utility, particularly with regard to biological subject matter has been extensively reviewed by both the Board of Patent Appeals and Interferences and the Court of Appeals for the Federal Circuit.

The Court of Appeals for the Federal Circuit has stated in Fujikawa v. Watanasin, 93 F.3d 1559, 1563, 39 USPQ2d 1895, 1898-99 (Fed. Cir. 1996):

> For over 200 years, the concept of utility has occupied a central role in our patent system. See Brenner v. Manson, 383 U.S. 519, 529, 148 USPQ 689, 693 (1966). Indeed, "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." Id. at 534, 148 USPQ at 695. Consequently, it is well established that a patent may not be granted to an invention unless substantial or practical utility for the invention has been discovered and disclosed. See Cross v. Iizuka, 753 F.2d 1040, 1044, 224 USPQ 739, 742 (Fed. Cir. 1985).

It was stated in Genentech Inc. v. Nova Nordisk A/S, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1995):

> Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.)

Whether an issue of utility is raised under 35 U.S.C. § 101 or § 112, first paragraph, the initial burden is on the Patent and Trademark Office to establish reasons why one skilled in the art would not believe the objected statements of utility and/or enablement in the specification. In re Brana 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995); In re Langer, 503 F.2d 1380, 1391, 183

USPQ 288, 297 (CCPA 1974); In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

In the appeal presented in this application, applicants would urge that the Examiner has failed to establish those facts or provide that evidence which would reasonably support a conclusion that the present claimed invention is lacking in utility. A review of the application, including the claims and Specification results in the following finding of facts relative to the issue of utility.

Fact 1. The claims are directed to a product which is defined or characterized by the nucleotide sequence of the product (Claim 4), a vector which comprises the molecule of claim 4 (Claim 8), a host cell which contains the vector of claim 8 (Claim 9), a process for producing a polypeptide by culturing the host cell of claim 9 (Claim 24), an isolated polynucleotide consisting of the nucleotide sequence of SEQ ID NO:1 (Claim 25), an isolated polynucleotide consisting a nucleotide sequence of SEQ ID NO:3 (Claim 26), a vector as in claim 8 which is selected from the group consisting of a plasmid, virus, and bacteriophage (Claim 27), a vector as in claim 8 wherein said isolated nucleic acid molecule is inserted into said vector inproper orientation and correct reading frame such that the protein of SEQ ID NO:2 may be expressed by a cell transformed with said vector (Claim 28), a vector as in claim 28, wherein the isolated nucleic acid molecule is operatively linked to a promoter sequence (Claim 29) and an isolated nucleic acid molecule consisting of a nucleotide sequence that is completely complementary to a nucleotide sequence of claim 4 (Claim 30).

Fact 2. The specification specifically sets forth an extensive list of uses for the nucleotide molecule of claim 4 at pages page, first full paragraph and pages 39-45.

Fact 3. The Specification specifically sets forth an extensive list of uses for the polypeptide encoded by the nucleotide molecule of claim 8 at pages 22-32 of the specification.

Fact 4. The Specification explicitly describes how to use the nucleotide molecule for each utility mentioned.

Fact 5 The Specification explicitly describes a significant list of uses for the expressed polypeptide as well as how to use the polypeptide for these purposes.

Fact 6 The examiner has provided no evidence or established no facts which would reasonably support the conclusion that the present claimed invention lacks utility.

As stated in In re Oetiker, 977 F2.d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992): "[T]he examiner bears the initial burden, on review of the prior at or on any other ground, of presenting a *prima facie* case of unpatentability. If that burden is met, the burden of coming forward with evidence or arguments shifts to the applicants. If examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent."

On the facts of this case and after all of the evidence has been considered it should be clear that the examiner has failed to produce that evidence or demonstrate those facts which would reasonably support a rejection of the instant claims under 35 U.S.C. § 101.

In rejecting the claims of this application the examiner has addressed certain of the stated utilities present in the Specification as filed. Applicants would note that those seven uses addressed by the examiner make up only a small number of uses explicitly provided in the Specification. With regard to the use of the protein expressed by the claimed nucleotide sequence molecule, applicants would reference pages 22-32 of the Specification which sets forth a detailed description of the uses for the protein as well as details on how those uses can be accomplished. In

addition, applicants would note page 18, first full paragraph, as well as the material at pages 39-45 which specifically address the use of the nucleotide molecule of claims 4, 25 and 26. Similarly, at pages 49- 54 the Specification describes the use of vectors and host cells as claimed in claims 8, 9, 24, 27 28 and 29, as well as describing how these uses can be carried out.

Thus, in explaining the basis of the instant rejection, the examiner has addressed only a few of the many uses provided by applicants for the claimed invention.

However, even as to those uses which the examiner discusses, the examiner has acknowledged in each case that the uses are credible. However, the examiner urges that the uses are not "specific" and "substantial". Applicants disagree with this conclusion. Initially, applicants would urge that the examiner has not demonstrated with evidence or sound scientific reasoning why the many uses disclosed for the claimed invention should not be regarded as both "specific" and "substantial". It is difficult to understand how a description that the claimed nucleic acid molecule can be used for any of the various listed and described utilities could be anymore "specific." Similarly, it would reasonably appear that the issue as to whether a particular utility is "substantial" would reside in the eye of the beholder. This term, while not defined in its legal application to the utility requirement, would reasonably appear to be a qualitative term subject to opinion by the observer rather than a quantitative term which is easily evaluated. However, it seems clear that since the burden is on the examiner to establish a *prima facie* case to support a rejection of claims in an application, the burden to define and explain the application of such a requirement must also reside on the examiner. It is difficult for applicants to argue that the conclusion reached by the examiner is incorrect if the standard to which the applicants and their disclosure of their invention is not specifically defined and explained. No such explanation has

been provided by the examiner. In the absence of such a definition of the term "substantial" applicants would urge as an acceptable meaning the definition provided by the New Illustrated Webster's Dictionary of the English Language, 1992, page 961, Pamco Publishing Co., Inc. New York, New York, which would suggest that something is "substantial" if it is "[o]f or pertaining to substance; having real existence; not illusory; actual; permanent; lasting." Under this definition, then it can be seen that those listed uses presented in the Specification in support of the presently cliamed invention are "substantial."

The examiner has expressed the conclusion in discussing the seven listed utilities that:

Since this asserted utility is not present in mature form so it could be readily used in the real world sense, the asserted utility is not substantial." (OA, page 4).

Applicants are not aware of any statutory provision or law which would require that the stated utility for an invention must be "present in mature form so it could be readily used in the real world sense". To the extent that the examiner is suggesting that it must be capable of use on the date of filing of the application, applicants would urge that such an interpretation is not real world. For example, many pharmaceuticals are patented every year with indications in the specification as to the potential use of those products in treating humans. Yet, all must go through the FDA approval process, which is a lengthy process, before they can be used to treat humans. Clearly, such inventions meet the utility requirement of 35 U.S.C. § 101 and yet are not "in mature form so it could be readily used in the real world sense."

It would appear that the examiner's concern and therefore the basis of this rejection resides in the examiner's determination that applicants have not established that the protein, which is expressed by the claimed nucleic acid molecules, has the activity attributed it by the Specification. Applicants would point out that the nucleic acid molecule has utility in its own right. (Note pages

39-45). However, applicants acknowledge that the reason that the nucleic acid molecule is the focus of the present invention on appeal is its demonstrated ability to encode, under the appropriate conditions, the protein which we have identified as a G-protein coupled receptor. Further, applicants have determined that this protein is a member of a family of similar acting proteins. In the paragraph bridging pages 2-3 of the Final rejection (Paper No. 20) the examiner has acknowledged that:

[t]he claims are directed to a nucleotide that encodes a protein that possess approximately 100% homology to a known and well-characterized tyramine receptor, Tar1 (Bunzow, et al. 2001, Mol. Pharmacol., 60:1181-1188; Bunzow et al., 2003, Accession No. NM_138327). The Tar1 receptor has been studied extensively, and has a unqiue and specific pharmacological and physiological profile establishing it amoung the "trace-amine" receptors that respond to tyramine or phenethylamine (Bunzow et al. 2001, see Figure 2A). As suggested by Bunzow, et al, such receptors are partly responsible for the severe parasympathetic stimulation seen after ergot poisoning."

The examiner does not explain why, one skilled in this art knowing that the protein expressed by the presently claimed nucleotide molecule is approximately 100% homologous to this well known protein receptor, would be expected to lack the pharmacological and physiological profile of the known substance. In stead the examiner offers the unsupported generalization that "no well-established utility exists for newly isolated complex biological molecules." (e.g., Final Rejection, page 3, first full paragraph.) This statement is difficult to understand since many newly isolated complex biological molecules are proven to be useful for all kinds of purposes. At page 4, first full paragraph, the examiner even agrees that "the disclosed receptor as originally filed could be considered a G protein-coupled receptor", but urges that "no information is given in the Specification that would suggest that the disclosed polypeptide of SEQ ID NO: 2 is the *Tar1* G-protein-coupled receptor (Bunzow, et al. 2001) that responds to tyramine or phenethylamine and has a specific function within an organism." Thus, the examiner would appear to be requiring that,

despite the extensive description given in the Specification concerning this protein expressed by the claimed nucleic acid molecules, that applicants must submit further data in support of the statements in the specification. However, the Federal Circuit has noted that such request for additional evidence is appropriate "[o]nly after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." In re Brana, 51 F3.d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

It is applicants' position that the examiner has not yet met that burden which would suggest that one skilled in this art would doubt the asserted utilities based on the present detailed disclosure and the information provided both as to the use of the nucleic acid molecule itself or the protein which it is capable of expressing.

The only piece of evidence provided by the examiner in support of the present position taken is the article by Ji et al. (Ji, et al. 1998, J. Biol. Chem., 273 (28): 17299-17302) (See Final Rejection, page 4), which the examiner cites to demonstrate that the G protein-coupled receptor is a large class of receptors, the members of which have many functions within organisms. Applicants would not disagree with the characterization of the article. However, there is nothing in the article which would suggest that the protein expressed by the present claimed nucleotide molecule is unlikely to have the activity described in the Specification. Similarly, there is nothing present in this article which would reasonably be read to suggest that a protein having 100% homology to the known protein *Tar1* would not also be expected to possess the same pharmacological and physiological profile of the known protein.

The examiner has urged (Final Rejection, page 3) that "The specification does not discuss

evidence nor disclose experiments that impart any function for the polypeptide encoded by the claimed nucleotides in the context of the cell or organism." To the extent that the examiner is suggesting a requirement for experimentation data as to the activity of the encoded protein receptor or even the need to demonstrate such activity in the context of a cell or organism, applicants are not aware of any such requirement either statutory or based on case law relating to the utility requirement and the examiner has cited no authority which would reasonably support such a requirement.

On this record, it appears clear that the examiner has failed to provide evidence or pointed to those facts which would reasonably support the conclusion that the present Specification does not adequately meet the requirements of 35 U.S.C. § 101 with regard to providing a statement of a credible, specific, and substantial utility. Therefore, applicants would, therefore, urge that the rejections of 4, 8, 9, and 24-30 under 35 U.S.C. § 101 be reversed.

The Rejection under 35 U.S.C. § 112, first paragraph:

The examiner has additionally rejected claims 4, 8, 9, and 24-30 under 35 U.S.C. § 112, first paragraph stating that (Final Rejection, page 2):

since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility . . . one skilled in the art clearly would not know how to use the claimed invention.

Further explanation of this rejection is found at pages 6-9 of the Office action of December 16, 2002 (Paper No. 20). The examiner urges that "the specification does not teach functional or structural characteristics of the amine receptor polypeptided recited in the claims" (Paper No. 20, page 6).

Applicants would respectfully disagree with this finding by the examiner. Initially,

applicants would point out the fact that the examiner, in the Final rejection (paragraph bridging pages 2-3) has acknowledged that the protein expressed by nucleotide molecules presently claimed has approximately 100% homology with the known and well characterized tyramine receptor, *Tar 1*. Further the examiner acknowledges that this known receptor has a known pharmacological and physiological profile. In addition, the Specification, at pages 9-11, provides extensive discussion of the activity of the proteins encoded by the presently claimed nucleotide molecule. For example, at page 9, the Specification states: "The proteins of the present inventions are GPCR that participate in signaling pathways mediated by the aminergic subfamily in cells that express these proteins." In addition, the Specification on numerous occasions notes that these proteins are expressed in fetal brain, brain, placenta, liver, stomach and kidney. Thus, the Specification provides an extensive discussion of the protein, its activities and also the methodology of taking the claimed nucleotide molecules and producing the proteins in question using accepted techniques known in the art.

As with the rejection under 35 U.S.C. § 101 discussed above, the concern of the examiner appears to focus on the lack of experimental data in the Specification, to establish the activity of the protein encoded by the claimed nucleotide sequence. Despite the information provided in the Specification, the examiner has focused on this lack of data and argued that it is not readily apparent that the protein of this invention possesses the activities and usefulness attributed to it by applicants. The examiner has submitted and references several articles in support of the premise that (Paper No. 20, pages 6-7):

the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowning the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function

(See Box 2, page 36). Similarly, Bork (200, Genome Research 10:398-400) state that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multifunctionality, resulting in underpredictions of functionality of a new protein and (2) over predictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al.(1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancertral gene. Brenner (1999, Trends in Genetics 15:132-133 argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologues must have different molecule and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

The examiner then concludes that (Paper No. 20, page 7):

based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recogniztion that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to make a biologically active amine receptor-like polypeptide without resorting to undue experimentation to determine what the specific biological activities of the polypeptide are.

With regard to the cited articles, applicants would note that they either do not relate to the type of protein here under consideration or in every case are describing situations where the level of homology is significantly less than the 100% homology that has been demonstrated on the present record and acknowledged by the examiner. Their value, other than as general teaching, is questionable at best and in applicants' opinion do not raise to the level which would reasonably suggest to one skilled in this art that the protein encoded by the claimed nucleotide molecule would not be expected to have the specific activity and usefulness described in the Specification of this application. In the absence of such evidence, there is no reasonable basis or support for the conclusion reached by the examiner that "the specification fails to teach the skilled artisan how to

make a biologically active amine receptor-like polypeptide without resorting to undue experimentation to determine what the specific biological activities of the polypeptide are." In fact, the present specification provides a detailed description of how to take the claimed nucleotide molecule, make a vector, and insert the vector into a host cell, culture the cell or cells in a manner to express the GPCR protein. (Note pages 49-57). The examiner has failed to address the actual disclosure present in the Specification and explain why this disclosure would not result in the protein in question.

In the Final rejection, at page 8, the examiner lists those factors normally addressed in making a rejection under 35 U.S.C. § 112, first paragraph based on lack of enablement. However, in truth, the examiner has never come to grips with the actual disclosure presented in the Specification in support of applicants' invention. The concern has always been the examiner's unsupported opinion that the protein encoded by the nucleotide molecule of the claims might not have the activity specifically attributed to it in the Specification. This does not rise to the level of a proper *prima facie* case of unpatentability.

In In re Brana, 51 F3.d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995), the Federal Circuit addressed the utility requirement in considering a rejection under 35 U.S.C. § 112, first paragraph. In that decision, the Court repeated language from In re Marzocchi, 439 F2d. 220, 223, 169 USPQ 367, 369 (CCPA 1971) to the effect that:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein** which must be relied on for enabling support. (Emphasis added).

On the facts of this case, the examiner has failed to provide a level of evidence or established facts

which would provide a reason to doubt the objective truth of the extensive disclosure of the invention provided by the present Specification. In the absence of such evidence or facts, a *prima facie* case of unpatentability or a conclusion of unpatentability can not exist. Therefore, applicants would urge that the rejection of claims 4, 8, 9, and 24-30 under 35 U.S.C. § 112, first paragraph, be reversed.

Conclusion:

Applicants have addressed each of the rejections raised by the examiner in the Final rejection. For the reasons set forth above, applicants would urge that the rejection of claims 4, 8, 9, and 24-30 under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, be reversed.

Respectfully submitted,

Date: March 26, 2004

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Appendix

Claim 4. An isolated nucleic acid molecule consisting of a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence that encodes a protein comprising the amino acid sequence of SEQ ID NO: 2;

(b) a nucleotide sequence consisting of the nucleic acid sequence of SEQ ID NO:1; and

(c) a nucleotide sequence consisting of the nucleic acid sequence of SEQ ID NO:3.

Claim 8. A nucleic acid vector comprising a nucleic acid molecule of claim 4.

Claim 9. A host cell containing the vector of claim 8.

Claim 13. A method for detecting the presence of a nucleic acid molecule of claim 4 in a sample, said method comprising:

contacting the sample with an oligonucleotide compising at least 20 contiguous nucleotides that hybridizes to said nucleic acid molecule under stringent conditions, wherein the stringent condition is hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SCC, 0.1% SDS at 50-65°C, and

determining whether the oligonucletotide binds to said nucleic acid molecule in the sample.

Claim 24. A process for producing a polypeptide comprising culturing the host cell of claim 9 under conditions sufficient for the production of said polypeptide from a nucleic acid molecule that encodes said polypeptide, and recovering said polypeptide from the host cell culture.

Claim 25. An isolated polynucleotide consisting of a nucleotide sequence set forth in SEQ ID

NO:1.

Claim 26 An isolated polynucleotide consisting of a nucleotide sequence set forth in SEQ ID NO:3.

Claim 27. A vector according to claim 8, wherein said vector is selected from the group consisting of a plasmid, virus, and bacteriophage.

Claim 28. A vector according to claim 8, wherein said isolated nucleic acid molecule is inserted into said vector in proper orientation and correct reading frame such that the protein of SEQ ID NO:2 may be expressed by a cell transformed with said vector.

Claim 29. A vector according to claim 28, wherein said isolated nucleic acid molecule is operatively linked to a promoter sequence.

Claim 30. An isolated nucleic acid molecule consisting of a nucleotide sequence that is completely complementary to a nucleotide sequence of claim 4.